Urticarial Vasculitis and Schnitzler Syndrome

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KEYWORDS

• Urticaria • Schnitzler syndrome • Interleukin-1 • Urticarial vasculitis
• Leucocytoclastic vasculitis • Myeloma

KEY POINTS

- Newly defined diagnostic criteria of urticaria vasculitis and Schnitzler syndrome.
- Better understanding of pathophysiology.
- New treatment options described.

INTRODUCTION

Urticarial vasculitis is no longer classified as part of urticaria in the current guidelines for urticaria due to the underlying nature of the disease. It is defined as a leukocytoclastic vasculitis that presents, clinically, with wheals. In contrast to the histamine-induced wheals in urticaria, the wheals in urticarial vasculitis are not fleeting but often stay for more than 24 hours and sometimes leave small patches of a brownish color due to microbleedings.

The disease may be seen as a stage between severe chronic spontaneous urticaria and leucocytoclastic vasculitis in association with autoimmune processes. Minimal histologic signs of vasculitis may also occur in chronic urticaria patients and in a series of 83 patients with chronic urticaria 10 exhibited histologic features of urticarial vasculitis.

The clinical picture of urticarial vasculitis is diverse, and more severely affected patients often exhibit hypocomplementemia. The typical age group consists of young to middle-aged women.[1]

Schnitzler syndrome is related to urticarial vasculitis. It is defined as a disease with a monoclonal mostly immunoglobulin IgM gammopathy, increased markers of systemic inflammation such as C-reactive protein (CRP), and the chronic appearance of wheals, which, on histopathological examination, often show signs of urticarial vasculitis.[2]

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CLINICAL ASPECTS

Skin Lesions and Symptoms

Both in urticarial vasculitis and in Schnitzler syndrome wheals are typically generalized in distribution and sometimes faintly red but often, especially in urticarial vasculitis, deeply red or purplish-red in color. Sometimes punctate purpura may be observed within the lesions. The major points of differentiation against wheals in chronic spontaneous urticaria are their duration and resolution. Urticarial vasculitis wheals generally persist for more than 24 hours and up to 72 hours (ie, longer than the wheals in chronic spontaneous urticaria) and they resolve, in many cases, by developing a mild residual hyperpigmentation with small signs of bleeding, which is not seen in chronic spontaneous urticaria unless vigorous rubbing or scratching has caused bruising. Like in urticaria, most patients experience pruritus at the sites of lesions but sometimes also complain of burning sensations.[1]

Extracutaneous Signs and Symptoms

In addition to the wheals, extracutaneous signs and symptoms are often observed in both urticarial vasculitis and Schnitzler syndrome. The variety of clinical and laboratory findings are summarized in **Boxes 1** and **2** and **Tables 1–3**.

Course of Disease and Prognosis

The clinical course of urticarial vasculitis is often benign with resolution of the disease within 1 year in 30% to 40% of patients. In Schnitzler syndrome, the disease is normally lifelong or chronic, although single cases have been reported whereby a permanent resolution of the disease was observed together with the resolution of monoclonal gammopathy.[3,4]

Other related diseases sometimes showing signs of urticarial vasculitis are Muckle-Wells syndrome and autoimmune diseases, such as systemic lupus erythematosus, Still disease, or Sjögren syndrome.

In Schnitzler syndrome one of the key clinical features is recurrent fever, which is seen in more than 90% of patients. Recurrent fever was already described by Dr Schnitzler in her first description of the disease in 1972.[5] Monoclonal gammopathy, a key feature of Schnitzler syndrome, is not necessarily present at disease onset and may occur only after several years. On the other hand, the 10-year risk of developing a lymphoproliferative disorder in patients with Schnitzler syndrome, in most

Box 1
Diagnostic signs of urticarial vasculitis

1. Idiopathic chronic urticaria, vessel damage, wheals lasting >24 h
2. Leukocytoclastic vasculitis on histology
3. Purpuric or erythema multiforme-like lesions
4. Clinical signs of multisystem disease (see **Table 1**)
5. ESR, circulating immune complexes, positive direct immunofluorescence, Ø serum complement (see **Table 2**)
6. Resistance to therapy with antihistamines
7. Serologic evidence of connective tissue disease (+double-stranded ANF; +lupus band on immunofluorescence)

Data from Czarnetzki BM. Urticaria. Berlin: Springer; 1986.

Box 2
Schnitzler syndrome: Strasbourg diagnostic criteria

Obligate criteria

- Chronic urticarial rash and
- Monoclonal IgM or IgG
- Minor criteria
- Recurrent fever[a]
- Objective findings of abnormal bone remodeling with or without bone pain[b]
- A neutrophilic dermal infiltrate on skin biopsy[c]
- Leukocytosis and/or elevated CRP[d]

Definite diagnosis if

- Two obligate criteria AND at least 2 minor criteria if paraprotein IgM, and 3 minor criteria if paraprotein IgG

Probable diagnosis if

- Two obligate criteria AND at least 1 minor criterion if IgM, and 2 minor criteria if IgG

[a] A valid criterion if objectively measured. Must be >38°C and otherwise unexplained. Occurs usually, but not obligatory, together with the skin rash.
[b] As assessed by bone scintigraphy, MRI, or elevation of bone alkaline phosphatase.
[c] Corresponds usually to the entity described as "neutrophilic urticarial dermatosis" (Medicine 2009;88:23–31); absence of fibrinoid necrosis and significant dermal edema.
[d] Neutrophils >10,000/mm^3 and/or CRP >30 mg/L.
From Simon A, et al. Schnitzler's syndrome: diagnosis, treatment, and follow-up. Allergy 2013;68(5):562–8; with permission.

cases Waldenström macroglobulinemia, is estimated to be 15%,[2] although it is unclear which patients are at increased risk.

As for diagnostic criteria for Schnitzler syndrome, there was no internationally accepted consensus for a long time until recently an expert meeting was organized; the results have been published in *Allergy* 2013 (Simon 2013). The publication summarizes the recent literature and the expert consensus suggests that Schnitzler syndrome should be suspected in patients usually older than 40 years with (1) wheals, (2) a monoclonal gammopathy, which defines the syndrome, but a suspicion of Schnitzler syndrome arises when any of the symptoms listed in **Box 2** are present with fever $\geq$38.5°C with no other apparent cause. On the other hand, as there is no single blood or laboratory test available for the definite diagnosis, it is also important to remember that monoclonal gammopathy of unknown significance is relatively common in elderly patients and co-occurrence can thus be by chance with chronic urticaria. Other diseases that need to be ruled out are adult-onset Still disease and cryopyrin-associated periodic syndromes, especially Muckle-Wells syndrome, which normally occurs at a younger age.

The definite diagnosis is therefore based on estimating the probability according to the so-called Strasbourg diagnostic criteria, as summarized in **Box 2**.

HISTOPATHOLOGY AND LABORATORY FINDINGS

The histologic and laboratory findings characteristic for urticarial vasculitis are summarized in **Box 1** and **Table 2**. Urticarial vasculitis must be confirmed histologically.

Table 1
Clinical symptoms of urticarial vasculitis

Organ	Frequency of Involvement (%)	Clinical Manifestation
Skin	100	Pruritic or burning wheals (lasting >24 h), angioedema, bullae, lesions resembling erythema multiforme, livedo reticularis, Raynaud phenomenon, purpura
Joints	75	Arthralgias, swelling, stiffness, arthritis of single or multiple joints
Kidneys	60	Hematuria, proteinuria, decreased creatinine clearance
Respiratory system	55	Chronic obstructive pulmonary disease, pleuritic chest pain, laryngeal edema
Eyes	35	Uveitis, episcleritis, conjunctivitis, loss of vision
Gastrointestinal tract	30	Nausea, vomiting, diarrhea, abdominal pain
Nervous system	12	Mononeuritis, myositis, seizures, pseudotumor cerebri, increased central nervous system pressure
Cardiovascular and hematological systems	5	Raynaud syndrome, carditis, lymphadenopathy, leukopenia, thrombocytopenia, anemia
General systemic	10	Fever

Data from Czarnetzki BM. Urticaria. Berlin: Springer; 1986.

The most important diagnostic feature of histopathology is the damage of the walls of the small superficial venules evidenced by endothelial swelling, obstruction of the vessel lumen, and extravasation of erythrocytes into the dermis. In addition, fibrinoid material can be detected in most cases around the vessel walls. Leukocytoclasia and neutrophilic as well as eosinophilic infiltration is frequently observed but not mandatory. Histopathology and laboratory findings in Schnitzler syndrome overlap with urticarial vasculitis and are summarized in **Table 3** and **Box 2**.

TREATMENT

In contrast to urticaria, antihistamines are usually ineffective in urticarial vasculitis and Schnitzler syndrome and should therefore no longer be used as monotherapy; however, they may alleviate some symptoms, especially in patients with mild forms of urticarial vasculitis and also in those patients with chronic spontaneous urticaria with an overlap expressing only some features of vasculitis.

In general, in the treatment of urticarial vasculitis nonsteroidal anti-inflammatory drugs, cytostatic drugs, such as azathioprine or cyclophosphamide, and antimalarials have proven to be beneficial.[6]

Almost all patients respond to systemically administered corticosteroids. However, because of their side effects, daily treatment with corticosteroids should not be considered first-line therapy.

Table 2
Laboratory changes in patients with urticarial vasculitis (frequency is shown in parentheses, if known)

Histopathology	Fibrinoid changes in vessel walls (88%) Tissue eosinophilia (63%) Leukocytoclastic vasculitis (61%) Erythrocyte extravasation (58%) Neutrophilic infiltration (58%) Edema of upper dermis (44%)
Immunopathology (direct IF)	Deposits of (a) IgM, IgG, IgA or (b) Clq, C4, C3 or (c) fibrinogen in vessel walls and at the dermoepidermal junction, 89% of specimens
Changes in peripheral blood	ESR (75%) CH50 (35%), Clq, C4, C3 (32%), C5 Circulating immune complexes, normal or decreased immunoglobulins, rarely positive: ANF, RF cryoglobulins, bacterial or viral antigens; rarely: leukopenia, thrombocytopenia
Autoantibodies against	Clq IL-1 IgE *Fcε*RI Thyroid microsomal antigens

Abbreviations: ANF, antinuclear factor; ESR, erythrocyte sedimentation rate; IF, immunofluorescence; RF, rheumatoid factor.

Data from Czarnetzki BM. Urticaria. Berlin: Springer, 1986. Chapter 8; and Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. J Am Acad Dermatol 1992;26(3 Pt 2):441–8.

Table 3
Clinical and biological findings in patients with Schnitzler syndrome

Clinical or Biological Finding	Prevalence (%)
Urticarial rash	100
Elevated ESR ($\geq$30)	95
Fever	93
Monoclonal IgM gammopathy	89
Kappa light chain	89
Arthralgia/arthritis	77
Leucocytosis ($\geq$10,000)	76
Bone pain	68
Abnormal bone morphology	62
Palpable lymph nodes	74
Pruritus	45
Liver and/or spleen enlargement	34

From Simon A, et al. Schnitzler's syndrome: diagnosis, treatment, and follow-up. Allergy 2013;68(5):562–8; with permission.

In treatment-resistant urticarial vasculitis, case reports suggest the use of interferon-α,[7] mycophenolate mofetil,[8] colchicine,[9,10] or a cyclophosphamide-dexamethasone pulse therapy.[11]

Treatment of Schnitzler syndrome has changed during the recent years. It is important to define the exact need for treatment together with the patient. It must be noted that the disease severity varies considerably between patients and also in individual patients over the time. Some patients experience daily symptoms, whereas others have flare-ups once or twice a year. Simon and coworkers,[12] during the above-mentioned consensus conference in Strasbourg, devised an algorithm with recommendations for treatment. Treatment needs to be adapted based on the results. Apart from the question of significant alterations in quality of life, it is important to measure CRP. If CRP is below 30 mg/L, it is regarded as only a low level of persistent inflammation/disease activity.

In these cases an observation and/or treatment choice of colchicine 1 to 2 mg/d, nonsteroidal anti-inflammatory drugs in case of flare-ups, and hydroxychloroquine is recommended. Most important is, however, to follow-up these patients preferably at quarterly intervals per year to ensure that the level of disease remains stable.

In those patients with significant alterations of quality of life or persistent elevation of markers of inflammation (CRP>30 mg/L), the recent awareness of changes in the interleukin (IL) -1β as a hallmark of the pathologic abnormality in this disease has led to new possibilities in treatment. Anakinra has become one of the standard drug therapies[13] but also Canakinumab[14,15] as well as Rilonacept[16] have been shown to be effective, safe, and well tolerated.

Although of Schnitzler syndrome is defined as an auto-inflammatory disease of late onset involving IL-1, not all patients respond to anti-IL-1 treatment, showing that other cytokines are involved. In a case study 3 patients who did not respond to anti IL-1 responded well to anti-IL-6 treatment.[14]

Although the role of anti-IL-1 therapy is now widely established in Schnitzler syndrome, it may also be a treatment option in severe urticarial vasculitis. The results of the first clinical trial in urticarial vasculitis, assessing the effects of the humanized monoclonal anti-IL-1β antibody, demonstrated that a single-dose treatment significantly reduced disease activity and markers of inflammation.[17]

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